IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application of:	Rittershaus and Thomas	
Serial No.:	09/529,762	**ON APPEAL**
Filed:	April 18, 2000	Group Art Unit: 1644
Entitled:	XENOGENEIC CHOLESTERYL ESTER TRANSFER PROTEIN (CETP) FOR MODULATION OF CETP ACTIVITY	Examiner: P. Huynh

Atty. Docket No.: TCS-420.1P US

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

BRIEF ON APPEAL

Sir:

Pursuant to 37 C.F.R. § 1.192, Appellants submit this Brief on Appeal in triplicate, setting forth the basis of their appeal from the final Office Action, mailed September 10, 2002 (Paper No. 10) finally rejecting Claims 40-48, 51, and 52 of the above-identified patent application.

Notice of Appeal pursuant to 37 C.F.R. § 1.191 was filed on March 13, 2003.

This Brief is accompanied by the filing fee under 37 C.F.R. § 1.17(c) and the fee for a five-month extension in the time for filing this Brief under 37 C.F.R. § 1.7(a)(5), making the deadline for filing, Tuesday, October 14, 2003. The Commissioner is authorized to charge any additional fees required in connection with the papers filed herewith to PTO Deposit Account No. 50-0268.

REAL PARTY IN INTEREST

Appellants hereby identify AVANT IMMUNOTHERAPEUTICS, INC., formerly T CELL SCIENCES, INC., a corporation organized and existing under the laws of the State of Delaware and having an office and place of business in Needham, Massachusetts, as the assignee of the invention disclosed in the present application.

RELATED APPEALS AND INTERFERENCES

There are no related applications or patents currently on appeal or involved any interference.

STATUS OF CLAIMS

The present application was filed with original Claims 1-37.

A Preliminary Amendment canceling Claims 1-37 and adding new Claims 38-52 was filed concurrently therewith.

The Examiner issued a six-way restriction requirement (Paper No. 6) on September 21, 2001, requiring Appellants to elect either a specific CETP amino acid sequence or a particular method directed to modulating the level of endogenous CETP in a mammal.

Appellants traversed the restriction requirement in a Response submitted October 22, 2001, but provisionally elected the invention of Group III (Claims 40-48, 51, and 52) directed to a method of modulating the level of endogenous active CETP in a mammal comprising administering to the mammal, a whole, non-endogenous xenogeneic CETP.

In the first Office Action on the merits (Paper No. 7), dated January 29, 2002, the Examiner made the restriction requirement final. In addition, the Examiner rejected Claims 40-48, 51, and 52 under 35 U.S.C. §112, first paragraph as non-enabled and not satisfying the written description requirement. The Examiner also rejected Claims 40-44, 45, 47, 51, and 52 under 35 U.S.C. §102(a) based on the disclosure of Kwoh et al., WO 96/39168.

Appellants submitted a Response on June 13, 2002.

The Examiner issued a final rejection on September 10, 2002. All rejections were maintained.

Appellants filed a Response on March 7, 2003 canceling non-elected Claims 38, 39, 49, and 50, and amending Claims 40 and 44. Appellants also filed a Notice of Appeal.

An Advisory Action issued on April 10, 2003 maintaining all rejections.

A set of appealed Claims 40-48, 51, and 52 appears in the attached Appendix.

STATUS OF AMENDMENTS

All of Appellants' amendments have been entered.

SUMMARY OF INVENTION

It is well known in the art that decreased susceptibility to atherosclerosis and related cardiovascular disease is generally inversely correlated with increased absolute levels of circulating high density lipoprotein (HDL) and also increased levels of HDL relative to circulating levels of very low density lipoprotein (VLDL) and low density lipoprotein (LDL) (see, e.g., p. 2, lines 10-15, of Appellants' specification). Cholesteryl ester transfer protein (CETP) mediates the transfer of cholesteryl ester from HDL to triglyceride-rich lipoproteins such as VLDL and LDL, and also mediate the reciprocal exchange of triglycerides from VLDL to HDL (see, e.g., p. 2, lines 16-21, of Appellants' specification). High CETP activity has been correlated with decreased levels of HDL-associated cholesterol and with increased levels of LDL-associated cholesterol and VLDL-associated cholesterol, which increased levels in turn are correlated with increased risk of cardiovascular disease (p. 2, lines 21-24, of Appellants' specification).

Human CETP is an abundant, circulating glycoprotein of 476 amino acids having the ability to bind cholesterol ester (CE), triglycerides, phospholipids, and lipoproteins. The region of CETP defined by the carboxy-terminal 26 amino acids has been shown to be especially important for neutral lipid binding involved in neutral lipid transfer (see, e.g., p. 3, lines 1-3, of Appellants' specification).

Appellants' invention relates to the concept of modulating or inhibiting endogenous CETP activity in a mammal in order to control the relative levels of lipoproteins and to decrease or prevent the development of atherosclerosis (see, p. 5, lines

17-22, of Appellants' specification). Appellants' novel approach, however, is not to directly regulate CETP activity by injection of inhibitory substances. Rather, Appellants' invention provides methods and compositions for actively immunizing a subject against endogenous CETP for the treatment or prevention of atherosclerosis in a mammal. In other words, Appellants propose to induce antibody recognition, by a subject's own immune system, of its own, endogenous (or "self") CETP. Such immune recognition of self has been demonstrated by Appellants to result in modulation and inhibition of CETP activity with beneficial effects (see, Example 1 of Appellants' specification). Specifically, as discussed more fully below, Appellants made the surprising discovery of a method whereby administration of a whole non-endogenous CETP in a mammal results in the generation of antibodies (autoantibodies) that recognize the mammal's (own) endogenous CETP, which in turn results in a drop in CETP levels (activity) in the bloodstream of the treated mammal to near zero, a concomitant increase in the bloodstream of HDL to near 100% of the total cholesterol and a decrease in LDL in the bloodstream to near zero. The methods of the invention to obtain such beneficial effects, i.e., modulating CETP activity to below 20% or making total cholesterol levels to be greater than 90% in the form of HDL-cholesterol, are covered by the appealed claims (see, Appendix A).

In particular, the claimed methods of the invention comprise administering to a human or animal a vaccine composition comprising a whole non-endogenous CETP, i.e., a CETP that is not native to the mammal to be vaccinated. The methods of the invention induce production of antibodies (i.e., autoantibodies) in an individual that specifically target and inhibit the individual's endogenous CETP to obtain the beneficial result of lipoprotein profiles (such as decreased CETP activity and an elevated level of HDL relative to LDL, VLDL, or total cholesterol) that are correlated with a decreased risk of atherosclerosis or to decrease or prevent development of atherosclerotic lesions. In particular, Appellants demonstrate that administration of a whole non-endogenous CETP as taught in the present specification directly results in:

-an 80%-100% reduction in CETP levels, i.e., CETP activity;

-an HDL-cholesterol level of 90%-100% of the total cholesterol; and

-a reduction in LDL-cholesterol to less than 10%, preferably 0%, of the total

cholesterol present in the bloodstream.

Figure 9 directly demonstrates that administration of a whole non-endogenous CETP in a mammal will elicit production of antibodies that react with the mammal's own, endogenous CETP. As seen in Figure 9, this reaction is shown to reduce levels of circulating CETP molecules or CETP activity to less than 20% of the activity seen in untreated animals, to increase the levels of circulating HDL to nearly 100% of the total lipoprotein present in the bloodstream, and to result in an unexpectedly low level of circulating LDL in the bloodstream to less than 10% of the total as compared with untreated subjects.

In addition, administration of whole non-endogenous CETP according to the present invention has been demonstrated to actually reduce the incidence of formation of atherosclerotic lesions in test animals (see, Example 1, p. 19, line 28, to p. 20, line 21, and Fig. 11).

In view of examples such as this, it is apparent that one skilled in the art may select any whole, non-endogenous CETP protein and test that protein for the ability to generate "self" antibodies against endogenous CETP, without requiring an undue amount of experimentation on the part of the skilled practitioner.

SUMMARY OF THE REFERENCE CITED BY THE EXAMINER

The following reference is relied on as the basis for the rejection under 35 U.S.C. §102(a) maintained by the Examiner:

Kwoh et al., WO 96/39168 (1996) [hereinafter "Kwoh"]

The Kwoh document describes a study of CETP activity wherein an 11-mer peptide having a sequence common in human and rabbit CETP (SEQ ID NO: 3) is tested for the ability to generate autoantibodies in rabbit and to reduce the level of endogenous CETP activity. Kwoh compares the effects of immunization with a toxoid-conjugated and non-conjugated peptide over the course of a 28-week period. According to Kwoh, the toxoid-conjugated peptide reduced the level of CETP activity in rabbits to a greater degree than the non-conjugated peptide. There is no demonstration in Kwoh of

immunizing an individual against their own CETP with a whole non-endogenous CETP protein, which immunization achieves the unexpected CETP activity, HDL-cholesterol levels, or LDL-cholesterol levels recited directly in the appealed claims.

ISSUES ON APPEAL

The issues remaining after the final rejection (Paper No. 10) are:

1. With respect to the final rejection of Claims 40-48 and 51-52 for lack of enablement under 35 U.S.C. §112, first paragraph, the Appellants' specification is admitted (1) to be enabling for a method of increasing the production of anti-CETP antibody by administering a whole recombinant human CETP to a rabbit for reducing CETP activity, increasing the HDL-cholesterol, and lowering LDL-cholesterol associated with atherosclerosis; (2) to disclose full-length human CETP (SEQ ID NO:1), full-length rabbit CETP (SEQ ID NO:3), and two full-length humanized rabbit CETPs (SEQ ID NOS: 5 and 6); and (3) to disclose that rabbit CETP, murine CETP or simian CETP may be used for administration to a human subject. **The issue** for decision on appeal is whether the specification is sufficient to enable a skilled person in the field of immunology to practice the methods of the appealed claims, that is, to select and administer to a mammalian subject a non-endogenous CETP in an amount effective to alternatively achieve one of the following: to reduce CETP activity below 20% (Claim 40), to reduce CETP activity essentially to 0 μg/ml of blood in the subject (Claim 41), to raise the level of HDL-cholesterol in the blood of the subject to where this level is greater than about 90% of total cholesterol (Claim 42), to raise the level of HDL-cholesterol to where the level is about 100% of total cholesterol (Claim 43), to reduce the level of LDL-cholesterol in the blood of the subject to where this level is less than 10% of total cholesterol (Claim 44), or to reduce the level of LDL-cholesterol to where essentially none of the total cholesterol is LDL-cholesterol (Claim 45).

2. With respect to the final rejection of Claims 40-48 and 51-52 for failing to provide a written description of the invention to satisfy 35 U.S.C. §112, first paragraph, **the issue** presented for decision on appeal is whether the Appellants' specification demonstrates that they were in possession of the invention at the time of filing.

3. With respect to the final rejection of Claims 40-45, 47 and 51-52 as anticipated by Kwoh under 35 U.S.C. §102(a), **the issue** for decision on appeal is whether the Kwoh publication teaches each and every element of each of the rejected claims.

GROUPING OF THE CLAIMS

1. With respect to the grounds of rejection for lack of enablement, Claims 40-48 and 51-52 stand or fall together.

2. With respect to the grounds of rejection for lack of a written description, Claims 40-48 and 51-52 stand or fall together.

3. With respect to the grounds of rejection for anticipation in view of the disclosure of Kwoh, each of the appealed Claims 40, 41, 42, 43, 44, and 45 recites a separate element that is not taught by Kwoh, and thus each claim is separately patentable in view of Kwoh. Claims 46, 48, 51, and 52 are multiply dependent from any of Claims 40-45 and will stand or fall together on the patentability of the base claims.

ARGUMENTS

Appellants respectfully submit that the rejections are in error for the following reasons:

1. The methods described and claimed in the present application demonstrate that administration of a whole non-endogenous CETP to a mammal results in the generation of autoantibodies directed against that mammal's endogenous CETP. The generation of these autoantibodies results in a marked decline in CETP activity, a sharp increase in circulating HDL levels, and a sharp decrease in circulating LDL levels in the bloodstream

of the treated mammal. A person skilled in the art would have no difficulty following the examples of the specification to similarly treat a mammalian subject with a non-endogenous CETP, then measure the results to note achievement of the response particularly recited in the appealed claims.

2. The present specification, considered in its entirety, clearly meets the criteria of the Guidelines set forth in 66 Fed. Reg. 1099 (2001) and clearly shows that Appellants were in full possession of their invention as claimed at the time this application was filed.

3. The reference cited by the Examiner does not teach or disclose the administration of a whole non-endogenous CETP in a mammal to generate autoantibodies to endogenous CETP that results in a decrease in CETP levels (activity) to below 20% that of the untreated subject, or in a marked increase in HDL-cholesterol levels to 90% to 100% of the total cholesterol, or in a decrease in LDL-cholesterol levels to below 10% to 0% of total cholesterol. Therefore, the Kwoh reference cannot be considered to anticipate the appealed claims under 35 U.S.C. §102(a).

The foregoing arguments are expanded below:

1. The specification satisfies the requirements of 35 U.S.C. §112, first paragraph, for the claimed subject matter.

Appellants assert that the objections raised and maintained by the Examiner throughout the prosecution of the present application demonstrates an overall misinterpretation of Appellants' teachings and seeks to impermissibly limit the scope of the subject matter which Appellants are entitled to claim.

The Examiner has maintained the rejection of Claims 40-48, 51, and 52 as overly broad and requiring undue experimentation based on the arguments set forth on pp. 3-9 of the final Office Action. In particular, the Examiner asserts that the specification does not enable the claimed methods comprising administering to "any" mammal "any" non-endogenous cholesteryl ester transfer protein (CETP) in an amount effective to reduce CETP activity in the blood to a level that is less than 20% of that in the untreated

mammal (Claim 40), to achieve an unexpectedly low level of circulating CETP, i.e., essentially 0μg CETP per milliliter of blood (Claim 41), or to achieve an anti-atherogenic lipoprotein profile in the blood of the mammal wherein there is an unexpectedly high level of HDL-cholesterol (Claims 42, 43) or unexpectedly low level of LDL-cholesterol (Claims 44, 45) circulating in the bloodstream. The Examiner further rejected as inadequately enabled Appellants' claimed methods as applied to humans (Claims 46, 48) or as employing a preferred group of whole, non-endogenous CETP molecules (Claim 47). Finally, the Examiner rejected as not enabled Appellants' claimed methods wherein adjuvants are employed (Claims 51, 52).

According to the Examiner,

> "Other than the specific polypeptides mentioned above for a method of inhibiting the endogenous CETP activity, the specification fails to provide any guidance as how to make and use *any* non-endogenous CETP for a method of modulating any endogenous CETP in any mammal . . . Given the indefinite number of undisclosed non-endogenous CETP protein, it is unpredictable which undisclosed non-endogenous CETP would be useful for a method of inhibiting any non-endogenous CETP activity associated with atherosclerosis." (See, final Office Action, pg. 4). (emphasis in original).

The essence of the Examiner's argument alleging a lack of enabling disclosure for Appellants' methods is that the specification does not contain an explicit disclosure of every mammalian CETP sequence and does not contain a working example of every mammalian CETP administered to every mammal. The Examiner concludes that without such disclosure, a person skilled in the art would only be able to repeat the working example of Appellants' specification, that is, to administer only the recombinant human CETP of SEQ ID NO: 1 to rabbits and then measure antiatherosclerotic effects. According to the Examiner, this teaching could not be expanded to any other mammalian subject using any other whole non-endogenous CETP not having the exact same sequence as SEQ ID NO: 1.

By the Examiner's standard (which is not the standard set by 35 U.S.C. §112), patent coverage is only available for an Appellants' specific examples (such as Example 1

in the present specification). More specifically, it appears that the Examiner fails to appreciate the knowledge and skill of persons skilled in this particular art and how the skilled practitioner in this field relies on data from well known mammalian models (e.g., rabbits, transgenic mice, transgenic rats) employed in biochemical and pharmacological studies of lipoprotein/cholesterol metabolism and treatments for atherosclerosis (see, e.g., Tall, *J. Lipid Res., 34*: 1255-1274 (1993), of record; Shih et al., *Molec. Med. Today* (Elsevier Science, Ltd., 1995), pp. 364-372, of record). By the Examiner's standard of patentability, no inventor could ever obtain useful patent coverage in this field unless a working example of each and every possible embodiment of the invention (i.e., trying every possible whole, non-endogenous CETP in every mammalian species) was actually printed in the application. This would be an impossible requirement to meet and is clearly not a requirement of United States patent law or practice. In fact, such an onerous and unreasonable standard has been expressly repudiated by the courts:

> "What the Patent Office is here apparently attempting is to limit all claims to the specific examples, notwithstanding the clear disclosure of a broader invention. This it may not do. As was stated in *American Anode, Inc. v. Lee-Tex Rubber Products Corp.*, 136 F.2d 581, 585 (7th Cir. 1943) (emphasis added).
>
> 'There is no doubt that a patentee's invention may be broader than the particular embodiment shown in his specification. A patentee is not only entitled to narrow claims particularly directed to the preferred embodiment, but also to broad claims which define the invention without reference to specific instrumentalities.' *Smith v. Snow*, 294 U.S. 1 [at pages 11 et seq.] 55 S.Ct. 279, 79 L. Ed. 721."

In re Anderson, 471 F.2d 1237, 1241, 176 USPQ 331, 333 (CCPA 1973) (emphasis added). See, also, *In re Goffe*, 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976) ("To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for 'preferred' materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress (citation omitted)"). Thus, Appellants submit that the teachings,

guidance, and examples of the specification clearly and adequately enable and describe persons skilled in this art to carry out the claimed methods.

Appellants' claims are directed to methods of using a whole, non-endogenous CETP to produce a particular, measurable, anti-atherogenic condition of unexpected proportions. In particular, Appellants have discovered that administering a whole, non-endogenous CETP to a mammal will elicit production of antibodies that react with the mammal's own, endogenous CETP resulting in:

- an unexpectedly low level of circulating CETP molecules (essentially no detectable CETP per ml of blood plasma) or of CETP activity below 20% of the activity in an untreated mammal, or
- an unexpectedly high level of blood cholesterol in the form of "good cholesterol", i.e., HDL-cholesterol greater than 90%, and as high as 100%, or
- an unexpectedly low level of blood cholesterol in the form of "bad cholesterol", i.e., LDL-cholesterol less than 10%, and as low as, essentially, none.

Examples of achieving such measurable results according to Appellants' claimed methods are provided in the specification, using a well known rabbit model for atherosclerosis (see, Example 1 beginning at p. 16, and Figure 9 (demonstrating the results outlined above) of the specification). In addition, when rabbits were switched to a high cholesterol (atherogenic) diet, rabbits vaccinated with a whole, non-endogenous CETP had a demonstrably lower incidence of atherosclerotic lesions (see, Figure 14).

The Examiner considered the claims as overly broad and requiring undue experimentation because a person skilled in the art allegedly would be unable to predict whether any whole, non-endogenous CETP would work in the claimed invention. However, nowhere has the Examiner provided any evidence that would reasonably contravene what Appellants have demonstrated, using an animal model for atherosclerosis that is well known and widely used by persons skilled in this art. The Examiner has not provided any facts to indicate why a person skilled in this art who reads Appellants' specification and follows the directions and teachings for carrying out the

essential steps of the claimed methods should not reasonably expect the *in vivo* results taught and demonstrated (e.g., in Example 1 and Figure 9) in Appellants' specification.

In fact, when pressed for a reason why one skilled in the art, by following the teachings disclosed in the present specification, would be unable to select, administer, and test a whole, non-endogenous CETP for the ability to generate autoantibodies against the treated individual's endogenous CETP, the Examiner states,

> ". . . there is no guidance as to which amino acid residues within the full length amino acid sequence of any undisclosed non-endogenous CETP from any mammal can be deleted, substitute[d] and whether the resulting modified non-endogenous CETP protein would maintain the same structure, much less in generating antibodies that bind specifically to any mammals endogenous CETP for a method of inhibiting any endogenous CETP . . ." (See, Advisory Action issued 4/10/03, pg. 4).

In contrast to the Examiner's speculation, Appellants have provided an *in vivo* working example that used the rabbit model for atherosclerosis, which is known and relied on by persons skilled in this art for studying and developing methods of treating atherosclerosis. Obviously, such models are used in this art to obtain a reasonable basis for understanding compositions and methods for treating mammalian, and especially human, coronary artery disease without the enormous expense and time limitations that would be necessary to study *every* mammal or test *every* possible sequence variation.

Testing and optimization for a particular mammalian species is not undue experimentation, and it is not required by the statute that an inventor in this art provide a species by species or sequence by sequence optimization for results to be reasonably understood and believed by persons skilled in this art, especially when the practice and expectation of those skilled in this art is to use an accepted animal model for atherosclerosis and follow routine procedures for testing those models and testing sequence variations based on the choice of the skilled practitioner.

Despite Appellants' demonstration of success in practicing the claimed invention in a format known and understood by those skilled in this art, the Examiner appears to

have focused on whether a person skilled in the art could select the correct non-endogenous CETP for *any* mammal treated according to the claimed methods. Appellants note that, except in the case of novel molecules, the inventive feature of the claimed **methods** does not reside in a particular non-endogenous CETP employed. Persons skilled in this art are assumed to already know or to know how to easily determine whether one CETP is the same or different, i.e., non-endogenous, from the endogenous CETP in a particular mammalian subject. Much is already known by persons skilled in this art regarding CETP molecules of various mammalian species (see, e.g., Tall, *J. Lipid Res.,* 34: 1255-1274 (1993) (review on CETP, of record)) and whether various mammalian species even express an authentic CETP molecule in the blood (see, e.g., Breslow, *supra*, at p. 8317; Ha et al., *Comp. Biochem. Physiol., 71B*: 265-269 (1982) (early survey of CETP activities in various mammalian species, of record).

Determination of whether a CETP molecule is non-endogenous to the subject to be treated according to the invention is within the skill in the art and, Appellants assert, rather simple to determine since any protein is either endogenous or non-endogenous to a particular species. Even if the source of a CETP molecule is unknown, determination of whether a mystery CETP is non-endogenous to a mammal to be treated is easily determined by those skilled in this art using no more than routine analytical procedures.

Such routine analytical procedures include, but are not limited to, molecular weight determinations on denaturing gels, various immunoblotting techniques to detect amounts and relatedness of various CETP molecular species (e.g., Western immunoblots, ELISA assays), amino acid sequence analysis, nucleotide sequence analysis, and CETP activity assays (see, e.g., Examples 1-3 in the present specification; Bisgaier et al., *J. Lipid Res., 34*: 1625-1634 (1993) (CETP assay); Drayna et al., *Nature, 327*: 632-634 (1987) (cloning and sequence analysis); Nagashima et al., *J. Lipid Res., 29*: 1643-1649 (1988) (cloning and sequence analysis); Ha et al., *Comp. Biochem. Physiol., 71B*: 265-269 (1982) (survey of CETP activity exhibited in various mammalian species), all of record). Such methods may be applied to all naturally occurring CETPs, including xenogeneic and allelic variants, which may be expressed in an individual mammalian species.

In addition, without cataloguing every possibility, Appellants submit that persons skilled in this art reasonably expect the existence of both xenogeneic and allelic variants of a mammalian protein, including the circulating protein, CETP. Furthermore, persons skilled in this art recognize that a non-endogenous CETP may be a non-naturally occurring molecule derived from a naturally occurring CETP, e.g., by modifying one or more amino acid residues using *in vitro* methods to more closely resemble, but not be identical to, the CETP of the mammal being treated, i.e., a "mammalianized", non-endogenous CETP molecule as discussed in the specification (see, e.g., p. 8, line 22, to p. 9, line 17) and illustrated by "humanized rabbit" CETPs of SEQ ID NOs:5 and 6. Accordingly, persons skilled in this art are able to select and determine a CETP that is non-endogenous to the CETP of a particular subject to be treated, without undue experimentation.

Appellants further note that persons skilled in the art who follow Appellants' teachings are able to quickly determine whether a particular desired anti-atherogenic effect as recited in Appellants' claims is achieved, i.e., by using such standard assays to determine the blood plasma levels of CETP (level of protein *per se*), CETP activity (level of transfer activity), cholesterol level, LDL-cholesterol level, and/or HDL-cholesterol level. Thus, neither the selection of a non-endogenous CETP nor the determination of whether the recited endpoints have been reached in practicing Appellants' claims require undue experimentation on the part of persons skilled in this art. The Examiner has not explained why skilled persons in this art cannot follow the direct examples of the specification, even substituting other mammalian subjects for rabbits and other CETP molecules non-endogenous to the subject, then determining in the same way as demonstrated whether a particular endpoint recited in a claim is reached. It is respectfully submitted that the ability to follow Appellants' demonstrations is well within the skill of persons skilled in this art.

Appellants note that for enablement under 35 U.S.C. §112, first paragraph, it is sufficient that a person skilled in the art is either shown by example or directed to obtain elements in a claim, even if the person may have to carry out some confirmatory experimentation using routine methodology. *See*, e.g., *Atlas Powder Co. v. E.I. Du Pont*

DeMours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984) (*citing W.L. Gore & Associates v. Garlock, Inc.*, 721 F.2d 1540, 1557, 220 USPQ 303, 316 (Fed. Cir. 1983), and *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976)).

The Examiner's entire argument focuses on what the present specification does or does not contain and focuses not at all on the capability of persons skilled in this art. The fact that every known mammalian CETP sequence is not included in the Appellants' disclosure is of no moment. A patent specification need not teach, and preferably omits, what is well known in the art. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F2d 1367, 1384, 231 USPQ 81 (CAFC 1986). In the present invention, Appellants claim a *method* of using whole CETP molecules to obtain a particular lipoprotein profile in a mammalian subject. The practitioner's knowledge of specific non-endogenous CETP molecules to use in the practice of the invention is *presumed*. What Appellants have discovered is that whole, non-endogenous CETP may be administered to a mammalian subject and result in endogenous CETP levels that are unexpectedly low, endogenous HDL levels that are unexpectedly high, and endogenous LDL levels that are unexpectedly low. *What is claimed* is a method for modulating one of these levels by administering a whole, non-endogenous CETP to a subject *so as to achieve such unexpected results*, that is, it is a requirement of the claims that specific levels of CETP activity, HDL-cholesterol, or LDL-cholesterol are obtained as the result of the use of whole, non-endogenous CETP regardless of that protein's amino acid sequence or structural characteristics.

Appellants have demonstrated the practice of their *method* in a well known and widely used animal model that is understood and accepted by those skilled in this art. Given the applicability and acceptability of this model of mammalian cardiovascular and immune responses, Appellants submit that persons skilled in this art, seeing the operation of Appellants' method in this model, would believe that additional mammals and additional CETPs would operate in a like manner. In other words, Appellants have chosen an experimental animal that is a *model* of mammalian cardiovascular disease and immune response; and practitioners of Appellants' invention will readily apply the example of the model to other mammalian subjects in accordance with the teaching of

Appellants' specification, AND such practitioners will believe that such application to other animals or humans will have comparable results as defined in Appellants' claims.

Appellants have concisely and clearly defined their method in the claims, and have defined and discussed all the claim terms in the specification and drawings. Given the level of skill in this art, Appellants submit that a person skilled in the art may repeat the working examples of Appellants' specification and, what is more, may without experimentation apply the same method to another mammal besides New Zealand White rabbits, and moreover, may without experimentation select other whole CETPs that are non-endogenous to the intended mammalian subject. Furthermore, in view of the carefully explained assays and the data presented in the examples section of the present application, Appellants submit that a person skilled in the art can determine whether the blood level of CETP activity, HDL-cholesterol, or LDL-cholesterol in a whole-CETP-vaccinated subject has reached less than 20% or 0 μg/ml, greater than 90% or 100%, or less than 10% or "essentially none", respectively, as expressly required by the appealed claims.

In view of this enabling disclosure *directed to the person skilled in the art*, it is incumbent on the Examiner to explain and provide evidence in support of his contention that the person skilled in the art is incapable of knowing what is well known in the art, incapable of following the steps of Appellants' working examples, and incapable of using Appellants' model as a model for other methods encompassed by the claims, which heretofore the Examiner has not provided.

The Examiner has pointed out that Appellants' specification does not include sequences and lists of mammalian subjects that are known in the art and necessary as starting materials as a prelude to practicing Appellants' method, but as pointed out above, that is not a requirement of 35 U.S.C. §112. The Examiner has *not* pointed out why a person skilled in the art would be unable to practice the invention as claimed, and that *is* required to make out a *prima facie* case of non-enablement.

For the foregoing reasons, Appellants respectfully submit that the present claims are sufficiently enabled to meet the standard required by 35 U.S.C. §112, first paragraph.

Therefore, reversal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

2. The specification satisfies the written description requirement under 35 U.S.C. §112, first paragraph

In the final Office Action, page 10, the Examiner has rejected Claims 40-48 and 51-52 under 35 U.S.C. §112, first paragraph, for the reason that the specification is deemed not to reasonably convey to the person skilled in the art that the inventors were in possession of the claimed invention at the time of filing, i.e., does not satisfy the written description requirement under 35 U.S.C. §112, first paragraph. The Examiner further directs the Appellants to the Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶1, "Written Description" Requirement, as published in the Federal Register, Vol. 66, No. 4, Jan. 5, 2001, pp. 1099-1111 (hereinafter "Guidelines").

According to those Guidelines, the analysis of possession of the invention is akin to proving complete conception of an invention in an interference:

> "However, it is acknowledged that if evidence typically provided to prove a complete conception is present in the specification as filed, it would be sufficient to show possession. The Federal Circuit has stated '[t]he conception analysis necessarily turns on the inventor's ability to describe his invention with particularity. Until he can do so, he cannot prove possession of the complete mental picture of the invention.' (citation omitted)" (Guidelines at pp. 1101-1102.)

In discussing the General Principles to be applied by Examiners regarding compliance with the written description requirement, the Guidelines state:

> "An Appellant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as *words*, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including *description of an actual reduction to practice*, or by showing that the invention was 'ready for patenting' such as by the disclosure of drawings or *structural chemical formulas* that show that the invention

> was complete, or by describing *distinguishing identifying characteristics* sufficient to show that the Appellant was in possession of the claimed invention." (endnotes omitted; italics and underlining added) (Guidelines at p. 1104.)

In the present application, there is an actual reduction to practice of treatment to reduce CETP activity, raise HDL above 90% to 100%, and to lower LDL to less than 10% to essentially none, using a whole, non-endogenous CETP vaccine according to the description. See, Example 1, pp. 16-20 of the application. The whole rhuCETP used in the examples is identified using a "structural chemical formula", namely, a complete amino acid sequence (SEQ ID NO:1). The use of the CETP of SEQ ID NO:1 to lower CETP activity below 20%, to raise HDL-cholesterol above 90%, and to lower LDL-cholesterol below 10% is described in detail. See, e.g., Example 1 and Figures 8 and 9. Thus, the specification contains a demonstration of possession of the invention using the primary indicator called for by the Guidelines, namely, "description of an actual reduction to practice."

For any embodiment of the present claims not specifically exemplified in the specification, Appellants have provided a description of "distinguishing identifying characteristics" of the invention, for example, by providing: a complete written description of methods of using whole CETP molecules as immunogens; the complete amino acid structures for whole human and rabbit CETP (SEQ ID NOs:1 and 3); and written descriptions of methods for assaying the effectiveness of the vaccine (1) to cause production of endogenous CETP-binding antibodies, (2) to cause increase in HDL-cholesterol levels, (3) to cause a decrease in free cholesterol or LDL-cholesterol levels, and (4) to cause reduction in the formation of atherosclerotic plaque on arterial surfaces. Accordingly, all of the recitations of the claims under examination have been described (in writing) with such particularity that a person skilled in the art would understand that the inventors were in possession of a full conception of every feature of the invention recited in the claims.

Clearly, the invention as defined in the present claims is supported by sufficient written description in the specification, if the claims are analyzed in accordance with the Guidelines cited by the Examiner.

The Examiner appears to require a written description of the use of every possible embodiment of whole, non-endogenous CETP to reduce CETP activity, raise HDL levels, or lower LDL levels in order to satisfy the written description requirement under 35 U.S.C. §112, first paragraph. A moment's reflection will satisfy the Board of Appeals that this is an impossible requirement that is neither required by 35 U.S.C. §112, first paragraph, nor sought from an analysis of the application conducted under the Guidelines. (See, also, *SRI International v. Matsushita Electric Corp. of America*, 774 Fd. 1107, 227 USPQ 577 (CAFC 1985), "The law does not require that an Appellant describe in his specification every conceivable and possible feature embodiment of his invention. The law recognizes that patent specifications are written for those skilled in the art, and requires only that the inventor describe the 'best mode' of making and using the invention known to him at the time.")

Accordingly, for the reasons set forth above, it is respectfully submitted that the present specification provides a written description sufficient to apprise a person skilled in the art that Appellants were in full possession of their invention as of the filing date. Consequently, the written description requirement of 35 U.S.C. §112, first paragraph, has been satisfied and the rejection based on that requirement should be reversed.

3. The Kwoh reference does not anticipate the claimed invention under 35 U.S.C. §102(a).

In the final Office Action, the Examiner maintained the rejection of Claims 40-44, 45, 47, 51, and 52 under 35 U.S.C. §102(a) as anticipated by Kwoh et al., WO 96/39168.

With respect to WO 96/39168, The Examiner stated:

> "The 96/39168 publication teaches a method of modulating the endogenous active cholesteryl ester transfer protein (CETP) in a mammal such as a rabbit comprising administering to said mammal a full-length human CETP of SEQ ID NO:1 of WO 96/39168, or a [toxoid] conjugated human CETP peptide, which are non-endogenous CETP, in an amount effective to stimulate an immune response such as anti-CETP antibody wherein said antibody inhibits the function of CETP such as reducing the CETP activity below 20% of that of the untreated mammal (See abstract, Fig 2, of WO 96/39168, in particular). The reference

> method comprises administer[ing] to the mammal with an adjuvant . . . The reference method decreases LDL-cholesterol to less than 16% of the total cholesterol in the serum (blood plasma), which is about 10% (See Table 1, page 11, in particular). The term "about" expands the claimed 10% of the total cholesterol to read on the reference 16%. . . .
>
> * * *
>
> "While the reference is silent that the reference method of administering to the mammal a whole non-endogenous CETP has the property of that recited in claims 41-43 and 45, the antibody directed against said non-endogenous CETP in the mammal and the functional properties of the reference antibody are the inherent property of the reference method. Therefore the claimed method appears to be the same as the prior art method. Since the Patent Office does not have the facilities for examining and comparing the method of the instant invention to those of the prior art, the burden is on Appellant to show the prior art method is different from the claimed method. . . Thus, the reference teachings anticipate the claimed invention"

(final Office Action, paragraph bridging pp. 11-12). For the reasons explained below, Appellants respectfully submit that Kwoh is insufficient to teach the invention as claimed.

For anticipation under 35 U.S.C. §102 by a printed publication, that publication must teach each and every element or aspect of the claimed invention. As explained in MPEP §2131:

> **"TO ANTICIPATE A CLAIM, THE REFERENCE MUST TEACH EVERY ELEMENT OF THE CLAIM**
>
> "'A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.' *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). 'The identical invention must be shown in as complete detail as is contained in the . . . claim.' *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989)." (emphasis in original).

Appellants' claimed methods comprise administering a whole, non-endogenous CETP to a mammal to achieve an anti-atherogenic condition characterized by heretofore unknown levels of CETP activity, HDL-cholesterol, or LDL-cholesterol in the blood of the mammal.

First, Appellants note that the Example, Figure 2, and Table 1 of Kwoh describe a study in which rabbits were injected with a free, linear, toxoid-conjugated or non-conjugated 11-mer CETP fragment having a sequence in common with human and rabbit CETP (see, Example 2, p. 8, line 5-p. 10, line 30 of Kwoh). Thus, unlike Appellants' invention as claimed, none of the rabbits in Kwoh was administered a whole, non-endogenous CETP protein, as is called for by each of the appealed claims.

Figure 2 of Kwoh shows the CETP activity in rabbits that received a free or toxoid-conjugated peptide relative to that in control rabbits that received saline. Rabbits that received free peptide showed a slight relative decrease of no more than 15% (i.e., exhibited at least 85% of the control level of CETP activity) and rabbits that received the conjugated peptides showed a relative decrease of not more than 40% (i.e., exhibited at least 60% of the control level of CETP activity). Thus, Figure 2 provides no data for a mammal that has been administered a whole, non-endogenous CETP, and, furthermore, the peptide vaccines of Kwoh are not reported to provide a blood plasma condition in which the level of CETP activity in a mammal falls below 20% of the level found in the untreated mammal. Figure 2 thus does not describe each and every element of Appellants' claimed methods, particularly with respect to Claim 40 and 41.

As with Figure 2, Table 1 on page 11 of Kwoh only provides data from Example 2 of Kwoh in which rabbits were administered a free peptide or a toxoid-conjugated peptide vaccine. The Examiner states that the data in Table 1 shows a lipoprotein profile in which about 16% of the total cholesterol is LDL-lipoprotein, apparently referring to the data for rabbits that received a free 11-amino acid peptide vaccine. Not only does Table 1 not provide any description or data of Appellants' claimed method, Table 1 does not even have one example of achieving the low level of LDL-cholesterol achieved by Appellants' method.

The Examiner provides no explanation for the interpretation of the claim term "less than 10%" as being met by the best case 16% LDL/Total cholesterol level calculated from Kwoh Table 1 data. Appellants submit that the term "less than 10%" sets a threshold including only values under 10% up to and not exceeding 10%. The 60% excess required to reach 16% from 10% is submitted to be significant and thus not encompassed within "less than 10%" in the context of the measurements involved. Moreover, Appellants point out that their invention calls for achieving a maximum value of 10% for LDL-cholesterol, showing data where LDL-cholesterol is essentially completely eliminated, whereas the 16% level noted by the Examiner is the minimum LDL-cholesterol value achieved according to Kwoh, with all other values reported in Table 1 being higher than 16%. Accordingly, Kwoh as a reference does not meet or suggest the teaching, "less than 10%", completely aside from the fact that the methods compared are different.

Furthermore, the Examiner's focus on the possible properties of the antibodies elicited in the method of Kwoh and those elicited in Appellants' claimed methods is misdirected. Persons of ordinary skill in this art who read Appellants' specification know the difference between administering a whole, non-endogenous CETP and administering the CETP peptide fragments and conjugates as described in Kwoh. The description of the peptides in Examples 1 and 2 of Kwoh clearly distinguishes the Kwoh teachings from the recitations of Appellants' claims. From consideration of Kwoh, the person of ordinary skill in the art is not informed that reduction of HDL-cholesterol to a level of less than 10% is possible to achieve; only by using a whole non-endogenous CETP immunogen according to Appellants' disclosure can such a low level of LDL-cholesterol be achieved. This may be due to a difference in the polyclonal response to a different immunogen (CETP fragment vs. full-length, non-endogenous CETP) or to some other scientific phenomenon unknown even to Appellants: It does not matter. Kwoh does not provide a method or means for meeting Appellants' invention. The essential steps for carrying out Appellants' claimed methods are not identical to the methods described in Kwoh; Appellants' invention simply does not involve administering a peptide of Kwoh to a

mammal, and the Kwoh reference does not come close to disclosing the specific endpoints expressly stated in any of Appellants' claims.

In conclusion, Kwoh's teaching is irrelevant to the steps that a person of ordinary skill in this art must actually perform to practice the method of Appellants' claims. Absent a teaching of each and every element of Appellants' claimed methods, Kwoh does not qualify as a reference to reject Appellants' claims as anticipated under 35 U.S.C. §102(a).

Accordingly, Appellants respectfully request that the Board reverse the final rejection under 35 U.S.C. §102(a).

CONCLUSION

Appellants respectfully submit that the Examiner has failed to make out a case of nonenablement under 35 U.S.C. §112, first paragraph because:

- Appellants clearly demonstrate that administration of a whole non-endogenous CETP is capable of generating autoantibodies to the endogenous CETP of a treated mammal which directly leads to a surprising decrease in CETP activity to near zero, or an increase in circulating levels of HDL-cholesterol above 90% to near 100% of the total cholesterol in the bloodstream, or a decrease in circulating levels of LDL-cholesterol below 10% to near zero.
- Appellants clearly demonstrate how to identify, select, and test <u>any</u> whole non-endogenous CETP regardless of amino acid sequence or protein structure for its efficacy to generate autoantibodies to endogenous CETP to control blood cholesterol levels.

Appellants respectfully submit that the Examiner has failed to make out a case for lack of a written description under 35 U.S.C. §112, first paragraph because:

- Appellants' specification provides a clear written description for all methods of modulating cholesterol levels set forth in the claims, namely, by demonstrating an actual reduction to practice of embodiments set forth in the claims and providing a description in words of other embodiments, thus showing full possession of the invention as claimed by the Appellants at the time of filing.

Appellants respectfully submit that the Examiner has failed to make out a *prima facie* case for anticipation under 35 U.S.C. §102(a) because:

- The cited reference does not teach each and every element of Appellants' claimed invention; specifically, the cited Kwoh reference does not teach the administration of a whole non-endogenous CETP that directly leads to a 90%-100% reduction in overall CETP activity, a cholesterol level comprised of 90%-100% HDL-cholesterol, or a total LDL-cholesterol level of 10%-0% of total cholesterol in the bloodstream of the treated mammal. Therefore, Appellants' invention is not anticipated by the cited Kwoh reference.

Accordingly, for the reasons set forth herein, the final rejections applied against appealed Claims 40-48, 51, and 52 under 35 U.S.C. §112 and §102(a) as set forth in the final Office Action of September 19, 2002 are in error and should be reversed by this Board.

Respectfully submitted,

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October 14, 2003
date

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Appealed Claims

40. A method of modulating the level of endogenous cholesteryl ester transfer protein (CETP) activity in a mammal comprising administering to the mammal a whole, non-endogenous CETP in an amount effective to reduce CETP activity below 20% of that of the untreated mammal.

41. A method of modulating the level of endogenous cholesteryl ester transfer protein (CETP) in a mammal comprising administering to the mammal a whole, non-endogenous CETP in an amount effective to achieve a level of essentially 0 μg of CETP per milliliter of blood of the mammal.

42. A method of modulating the level of HDL-cholesterol in a mammal comprising administering to the mammal a whole, non-endogenous cholesteryl ester transfer protein in an amount effective to achieve a lipoprotein profile wherein greater than about 90% of the total cholesterol in the blood of the mammal is HDL-cholesterol.

43. The method of modulating the level of HDL-cholesterol in a mammal according to Claim 42, wherein the mammal is administered a whole, non-endogenous cholesteryl ester transfer protein in an amount effective to achieve a lipoprotein profile wherein about 100% of the total cholesterol in the blood of the mammal is HDL-cholesterol.

44. A method of modulating the level of LDL-cholesterol in a mammal comprising administering to the mammal a whole, non-endogenous cholesteryl ester transfer protein in an amount effective to achieve a lipoprotein profile wherein less than 10% of the total cholesterol in the blood plasma of the mammal is LDL-cholesterol.

45. A method of modulating the level of LDL-cholesterol in a mammal comprising administering to the mammal a whole, non-endogenous cholesteryl ester transfer protein in an amount effective to achieve a lipoprotein profile wherein essentially none of the total cholesterol in the blood of the mammal is LDL-cholesterol.

46. The method according to any one of Claims 40-45, wherein the mammal is a human.

47. The method according to any one of Claims 40-45, wherein the whole, non-endogenous cholesteryl ester transfer protein (CETP) is selected from the group consisting of a xenogeneic CETP; an allelic variant of the mammal's endogenous CETP; and a mammalianized, non-endogenous CETP in which the amino acid sequence of a non-endogenous CETP has been altered by deletion or substitution of one or more amino acids so as to make the amino acid sequence of said non-endogenous CETP more similar to the mammal's endogenous CETP.

48. The method according to Claim 47, wherein the mammal is a human.

51. The method according to any one of Claims 40-45, wherein the whole, non-endogenous CETP is administered to the mammal in combination with an adjuvant, wherein the adjuvant is effective to non-specifically stimulate the immune response of the mammal.

52. The method according to Claim 51, wherein the adjuvant is selected from the group consisting of alum, Freund's Complete Adjuvant, Freund's Incomplete Adjuvant, and RIBI Adjuvant System.